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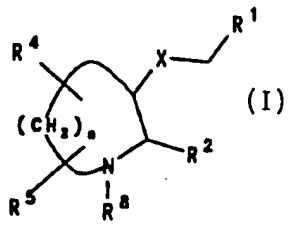
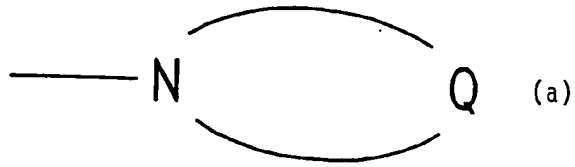



(I)




(a)

(57) Abstract

Compounds of Formula (I), and salts and prodrugs thereof, wherein n is 1, 2 or 3; X represents O or S; $R^1$ is optionally substituted phenyl; $R^2$ is aryl or heteroaryl; $R^4$ and $R^5$ are independently H, halo, $C_{1-6}$alkyl, oxo, $CH_2OR^a$, $CO_2R^a$ or $CONR^aR^b$; $R^8$ represents $C(COOR^a)_2$, $C(CONR^aR^b)_2$ or $C_{1-6}$alkyl substituted by $C(=NR^a)NR^bNR^cCO_2R^d$, $CONHNR^aR^b$, $C(S)NR^aR^b$, $CONR^aC_{1-6}alkylR^{12}$, $CONR^{13}C_{2-6}$alkynyl, $CONR^{13}C_{2-6}$alkenyl, $COCONR^aR^b$, $CONR^aC(NR^b)NR^cR^d$, $CONR^{13}SO_2R^a$, $SO_2NR^{13}COR^a$, $CONR^a$heteroaryl or $COR^q$; $R^a$, $R^b$, $R^c$ and $R^d$ are each H, $C_{1-6}$alkyl, phenyl or trifluoromethyl. $R^{12}$ represents $OR^a$, $CONR^aR^b$ or heteroaryl; $R^{13}$ represents H or $C_{1-6}$alkyl; and $R^q$ represents a group (a) where Q represents the residue of a non-aromatic azacyclic or azabicyclic ring system; are tachykinin antagonists useful in therapy.

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# AZACYCLIC COMPOUNDS

This invention relates to a class of azacyclic compounds, which are useful as tachykinin antagonists. More particularly, the compounds of the invention comprise an azacyclic ring system substituted by an arylmethyloxy or arylmethylthio moiety.

The tachykinins are a group of naturally-occurring peptides found widely distributed throughout mammalian tissues, both within the central nervous system and in the peripheral nervous and circulatory systems. The structures of three known mammalian tachykinins are as follows:

Substance P:

Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-$NH_2$

Neurokinin A:

His-Lys-Thr-Asp-Ser-Phe-Val-Gly-Leu-Met-$NH_2$

Neurokinin B:

Asp-Met-His-Asp-Phe-Phe-Val-Gly-Leu-Met-$NH_2$

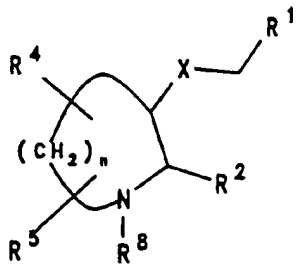
Evidence for the usefulness of tachykinin receptor antagonists in pain, headache, especially migraine, Alzheimer's disease, multiple sclerosis, attenuation of morphine withdrawal, cardivascular changes, oedema, such as oedema caused by thermal injury, chronic inflammatory diseases such as rheumatoid arthritis, asthma/bronchial hyperreactivity and other respiratory diseases including allergic rhinitus, inflammatory diseases of the gut including ulcerative colitis and Crohn's disease, ocular injury and ocular inflammatory diseases, proliferative vitreoretinopathy, irritable bowel syndrome and disorders of bladder function including cystitis and bladder detruser hyper-reflexia is reviewed in "Tachykinin Receptors and

Tachykinin Receptor Antagonists", C.A. Maggi, R. Patacchini, P. Rovero and A. Giachetti, J. Auton. Pharmacol. (1993) 13, 23-93. Tachykinin antagonists are also believed to be useful in allergic conditions [Hamelet et al Can. J. Pharmacol. Physiol. (1988) 66 1361-7], immunoregulation [Lotz et al Science (1988) 241 1218-21 and Kimball et al, J. Immunol. (1988) 141 (10) 3564-9], and as anticonvulsants [Garant et al., Brain Research (1986) 382 372-8]. Tachykinin antagonists may also be useful in the treatment of small cell carcinomas, in particular small cell lung cancer (SCLC) [Langdon et al., Cancer Research (1992) 52, 4554-7].

It has furthermore been suggested that tachykinins have utility in the following disorders: depression, dysthymic disorders, chronic obstructive airways disease, hypersensitivity disorders such as poison ivy, vasospastic diseases such as angina and Reynauld's disease, fibrosing and collagen diseases such as scleroderma and eosinophillic fascioliasis, reflex sympathetic dystrophy such as shoulder/hand syndrome, addiction disorders such as alcoholism, stress related somatic disorders, neuropathy, neuralgia, disorders related to immune enhancement or suppression such as systemic lupus erythmatosis (European patent application no. 0 436 334), conjuctivitis, vernal conjunctivitis, contact dermatitis, atropic dermatitis, urticaria, and other eczematoid dermatitis (European patent application no. 0 394 989) and emesis (European patent application no. 0 533 280).

European patent application no. 0 436 334 discloses 4- to 7-membered azacyclic compounds substituted at the 3-position by a substituted amino moiety. The compounds are said to be tachykinin antagonists.

The present invention provides a compound of formula (I), or a salt or prodrug thereof:



(I)

wherein

n is 1, 2 or 3;

X represents O or S;

$R^1$ represents phenyl optionally substituted by 1, 2 or 3 groups selected from $C_{1-6}$alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$alkynyl, halo, cyano, nitro, trifluoromethyl, trimethylsilyl, $-OR^a$, $SR^a$, $SOR^a$, $SO_2R^a$, $-NR^aR^b$, $-NR^aCOR^b$, $-NR^aCO_2R^b$, $-CO_2R^a$ and $-CONR^aR^b$;

$R^2$ represents aryl selected from phenyl and naphthyl; heteroaryl selected from indazolyl, thienyl, furyl, pyridyl, thiazolyl, tetrazolyl and quinolyl; benzhydryl; or benzyl; wherein each aryl or heteroaryl moiety may be substituted by $C_{1-6}$alkyl, $C_{1-6}$alkoxy, halo or trifluoromethyl;

$R^4$ and $R^5$ may be present on any available carbon atom of the azacyclic ring and each independently represent H, halo, $C_{1-6}$alkyl, oxo, $CH_2OR^a$, $CO_2R^a$ or $CONR^aR^b$;

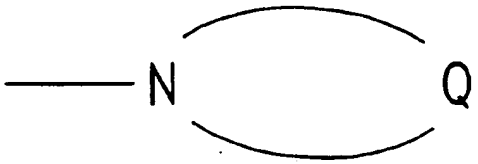
$R^8$ represents $C(COOR^a)_2$, $C(CONR^aR^b)_2$ or $C_{1-6}$alkyl substituted by $C(=NR^a)NR^bNR^cCO_2R^d$, $CONHNR^aR^b$, $C(S)NR^aR^b$, $CONR^aC_{1-6}alkylR^{12}$, $CONR^{13}C_{2-6}$alkynyl, $CONR^{13}C_{2-6}$alkenyl, $COCONR^aR^b$, $CONR^aC(NR^b)NR^cR^d$, $CONR^{13}SO_2R^a$, $SO_2NR^{13}COR^a$, $CONR^a$heteroaryl or $COR^q$;

$R^a$, $R^b$, $R^c$ and $R^d$ each independently represent H, $C_{1-6}$alkyl, phenyl or trifluoromethyl.

$R^{12}$ represents $OR^a$, $CONR^aR^b$ or heteroaryl;

$R^{13}$ represents H or $C_{1-6}$alkyl; and

$R^q$ represents a group



where Q represents the residue of a non-aromatic azacyclic or azabicyclic ring system.

As used herein, the definition of each expression, when it occurs more than once in any structure, is intended to be independent of its definition elsewhere in the same structure.

The alkyl, alkenyl and alkynyl groups referred to with respect to the above formula may represent straight, branched or cyclic groups, or combinations thereof. Thus, for example, suitable alkyl groups include methyl, ethyl, n- or iso-propyl, n-, sec-, iso- or tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, and cycloalkyl-alkyl groups such as cyclopropylmethyl; suitable alkenyl groups include vinyl and allyl; and suitable alkynyl groups include propargyl.

The term "halo" as used herein includes fluoro, chloro, bromo and iodo, especially chloro and fluoro.

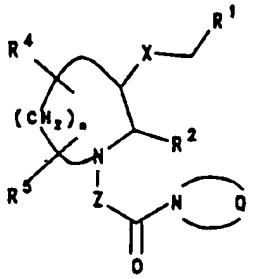
The present invention includes within its scope prodrugs of the compounds of formula (I) above. In general, such prodrugs will be functional derivatives of the compounds of formula (I) which are readily convertible <u>in vivo</u> into the required compound of formula (I). Conventional procedures for the selection and

preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

The compounds according to the invention may exist both as enantiomers and as diastereomers. In particular, the relative orientation of the 2- and 3-substituents on the azacyclic ring may give rise to cis and trans diastereoisomers, of which the cis stereochemistry is preferred. It is to be understood that all such isomers and mixtures thereof are encompassed within the scope of the present invention.

One subgroup of compounds according to the invention is represented by compounds of formula (I) wherein $R^4$ and $R^5$ each independently represent H, halo, $C_{1-6}$alkyl, oxo, $CO_2R^{10}$ or $CONR^{10}R^{11}$; $R^8$ represents $C_{1-6}$alkyl substituted by a group selected from $CONHNR^aR^b$, $C(S)NR^aR^b$, $CONR^aC_{1-6}alkylR^{12}$, $CONR^{13}C_{2-6}$alkynyl, $CONR^{13}C_{2-6}$alkenyl, $COCONR^aR^b$, $CONR^aC(NR^b)NR^aR^b$, and $CONR^a$heteroaryl; and salts and prodrugs thereof.

A further subgroup of compounds according to the invention is represented by compounds of formula (Ia):




(Ia)

wherein n, X, $R^1$ and $R^2$ are as defined for formula (I); Q is the residue of an azacyclic or a bridged azabicyclic ring system;

Z represents an alkyl chain of 1, 2, 3, 4, 5 or 6 carbon atoms; and

$R^4$ and $R^5$ each independently represent H, halo, $C_{1-6}$alkyl, oxo, $CO_2R^a$ or $CONR^aR^b$; and salts and prodrugs thereof.

Preferably n is 2 or 3, more preferably 3.

Preferably X represents O.

Preferably $R^1$ represents substituted phenyl. When $R^1$ is substituted phenyl suitable substituents include nitro, trifluoromethyl, trimethylsilyl, bromo, chloro, fluoro, iodo, cyano, $C_{1-6}$alkyl such as methyl, ethyl, i-propyl, i-butyl, t-butyl and cyclopropyl, $C_{2-6}$alkenyl such as vinyl, $C_{1-6}$alkoxy such as methoxy, ethoxy and i-propoxy, phenoxy, amino, carboxamido and carbonylmethoxy. Preferably $R^1$ represents phenyl substituted by one or more groups selected from $C_{1-4}$alkyl, such as methyl and t-butyl, trifluoromethyl and halo such as iodo, bromo chloro and fluoro.

Suitably $R^1$ represents monosubstituted phenyl, such as 3-substituted phenyl or, preferably, disubstituted phenyl, such as 3,5-disubstituted phenyl. Preferably $R^1$ represents phenyl substituted at the 3-position by trifluoromethyl or a $C_{1-6}$alkyl group such as t-butyl, or 3,5-disubstituted phenyl wherein the substituents are independently selected from trifluoromethyl, chloro, fluoro, methyl and t-butyl. Particularly preferred is 3,5-bis(trifluoromethyl)phenyl.

Suitably $R^2$ represents benzhydryl or optionally substituted phenyl, such as phenyl optionally substituted by halo such as fluoro or chloro, preferably in the 3-position. Preferably $R^2$ represents unsubstituted phenyl or unsubstituted benzhydryl, more preferably unsubstituted phenyl.

Suitable values for $R^4$ and $R^5$ include H, $C_{1-6}$alkyl, especially methyl, hydroxymethyl and oxo. The substitutents $R^4$ and $R^5$ may be located on any available carbon atom of the azacyclic ring including, except in the case where the substituent $R^4$ or $R^5$ in question represents oxo, C-2 and C-3. Preferably at least one of $R^4$ and $R^5$ represents H. In one preferred group of compounds $R^4$ and $R^5$ both represent H. In a further preferred group of compounds one of $R^4$ and $R^5$ is H and the other of $R^4$ and $R^5$ is methyl, preferably 2-methyl.

Suitable values for $R^8$ include $C(COO(C_{1-6}alkyl))_2$, such as $C(COOCH_3)_2$, $C(CONH_2)_2$ and $C_{1-6}$alkyl, preferably $C_{1-4}$alkyl, more preferably $CH_2$ or $CH(CH_3)$, substituted by $C(=NH)NHNHCO_2C_{1-6}$alkyl, $CONHNH_2$, $COCONH_2$, $CONHC(NH)NH_2$, $C(S)NH_2$, $CONR^{13}C_{2-6}$alkynyl, $CONR^aC_{1-6}alkylC_{1-6}$alkoxy, $CONHSO_2C_{1-6}$alkyl, $CONR^aC_{1-6}$alkylheteroaryl, $CONR^a$heteroaryl or $COR^q$.

When $R^8$ represents $C_{1-6}$alkyl subsituted by $CONR^aC_{1-6}$alkylheteroaryl or $CONR^a$heteroaryl, the heteroaryl moiety will suitably be selected from thienyl, furyl, pyridyl, thiazolyl, tetrazolyl, pyrrolyl, pyrazolyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, quinolyl, triazolyl, oxazolyl, oxadiazolyl, thiadiazolyl, isoxazolyl, isothiazolyl, benzoxazolyl, imidazolyl, benzimidazolyl, benzothiophenyl, benzofuranyl, and indolyl, preferably, furyl and pyridyl. The heteroaryl moiety may be optionally substituted. Suitable substituents include one or more of $C_{1-6}$alkyl, $C_{1-6}$alkoxy, phenyl, oxo, thioxo, halo, trifluoromethyl, $NR^aR^b$, $NR^aCOR^b$, $CONR^aR^b$, $SR^a$, $SO_2R^a$, $CO_2R^a$ and $CH_2OR^a$, where $R^a$ and $R^b$ are as previously defined.

The non-aromatic azacyclic or azabicyclic ring system of which Q forms the residue may contain, in addition to the nitrogen atom through which the ring is

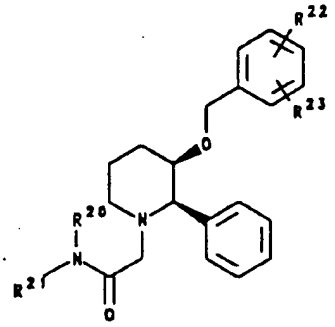
linked to the carbonyl moiety of the group $COR^q$, a further heteroatom selected from O and S, or a group $NR^{18}$, where $R^{18}$ is H or $C_{1-6}$alkyl.

When Q forms the residue of an azacyclic ring system, the azacyclic ring system will suitably contain from 5 to 9 ring atoms, preferably 5, 6 or 7 ring atoms, more preferably 6.

When Q forms the residue of an azabicyclic ring system, the azabicyclic ring system will suitably contain from 7 to 10 ring atoms, preferably 6 or 8 ring atoms, more preferably 8.

Suitable examples of the ring system of which Q forms the residue include pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, N-methylpiperazinyl azabicyclo[2.2.2]octanyl and azabicyclo[3.2.2]nonyl, preferably piperidyl, morpholinyl or N-methylpiperazinyl, more preferably morpholinyl or N-methylpiperazinyl.

A preferred subgroup of compounds according to the invention is represented by compounds of formula (Ib), and salts and prodrugs thereof.

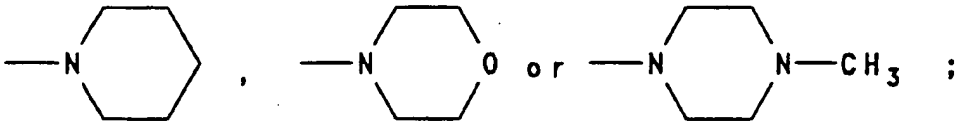


(Ib)

wherein

$R^{20}$ represents H or $C_{1-6}$alkyl, preferably H or methyl;

$R^{21}$ represents $NH_2$, $C(=NH)NH_2$, $C_{2-6}$alkynyl or $C_{1-6}$alkyl substituted by $C_{1-6}$alkoxy, such as methoxy or heteroaryl, such as furyl or pyridyl; or $R^{20}$ and $R^{21}$ together with the nitrogen atom to which they are attached form a group



$R^{22}$ and $R^{23}$ independently represent H $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, halo, cyano, nitro, trifluoromethyl, trimethylsilyl, $OR^a$, $SR^a$ $SOR^a$, $SO_2R^a$, $NR^aR^b$, $NR^aCOR^b$, $NR^aCO_2R^b$, $COR^a$ or $CONR^aR^b$, where $R^a$ and $R^b$ are as previously defined.

For use in medicine, the salts of the compounds of formula (I) will be pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the invention or of their pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable non-toxic acid such as hydrochloric acid, sulphuric acid, oxalic acid, fumaric acid, p-toluenesulphonic acid, maleic acid, succinic acid, acetic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid. Salts of amine groups may also comprise quaternary ammonium salts in which the amino nitrogen atom carries a suitable organic group such as an alkyl, alkenyl, alkynyl or aralkyl moiety. Thus, for example, when both $R^1$ and $R^2$ are other than hydrogen, the

nitrogen atom to which they are attached may be further substituted to give a quaternary ammonium salt. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include metal salts such as alkali metal salts, e.g. sodium or potassium salts; and alkaline earth metal salts, e.g. calcium or magnesium salts.

The present invention accordingly provides compounds of formula (I) and their pharmaceutically acceptable salts.

The present invention includes within its scope prodrugs of the compounds of formula (I) above. In general, such prodrugs will be functional derivatives of the compounds of formula (I) which are readily convertible in vivo into the required compound of formula (I). Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

The compounds according to the invention may exist both as enantiomers and as diastereomers. It is to be understood that all such isomers and mixtures thereof are encompassed within the scope of the present invention.

The substance P antagonising activity of the compounds described herein was evaluated using the human NK1R assay described in published European patent application no. 0 528 495. The method essentially involves determining the concentration of the test compound required to reduce by 50% the amount of radiolabelled substance P binding to human NK1R, thereby affording an $IC_{50}$ value for the test compound. The compounds of Examples 1-10, for example, were found to have $IC_{50}$ values less than 100nM.

The invention also provides pharmaceutical compositions comprising a compound of this invention in association with a pharmaceutically acceptable carrier. Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules, solutions or suspensions, or suppositories, for oral, parenteral or rectal administration, or topical administration including administration by inhalation or insufflation.

For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a non-toxic pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by

an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as set out above. Preferably the compositions are adminsitered by the oral or nasal respiratory route for local or systemic effect. Compositions in preferably sterile pharmaceutically acceptable solvents may be nebulised by use of inert gases. Nebulised solutions may be breathed directly from the nebulising device or the nebulising device may be attached to a face mask, tent or intermittent positive pressure breathing machine. Solution, suspension or powder compositions may be

administered, preferably orally or nasally, from devices which deliver the formulation in an appropriate manner.

For topical administration, for example as a cream, ointment or lotion, pharmaceutically acceptable carriers are, for example, water, mixtures of water and water-miscible solvents such as lower alkanols or arylalkanols, vegetable oils, polyalkylene glycols, petroleum based jelly, ethyl cellulose, ethyl oleate, carboxymethylcellulose, polyvinylpyrrolidone, isopropyl myristate and other conventionally-employed non-toxic, pharmaceutically acceptable organic and inorganic carriers. The pharmaceutical preparation may also contain non-toxic auxiliary substances such as emulsifying, preserving, wetting agents, bodying agents and the like, as for example, polyethylene glycols 200, 300, 400 and 600, carbowaxes 1,000, 1,500, 4,000, 6,000 and 10,000, antibacterial components such as quaternary ammonium compounds, phenylmercuric salts known to have cold sterilizing properties and which are non-injurious in use, thimerosal, methyl and propyl paraben, benzyl alcohol, phenyl ethanol, buffering ingredients such as sodium chloride, sodium borate, sodium acetates, gluconate buffers, and other conventional ingredients such as sorbitan monolaurate, triethanolamine, oleate, polyoxyethylene sorbitan monopalmitylate, dioctyl sodium sulfosuccinate, monothioglycerol, thiosorbitol, ethylenediamine tetraacetic acid, and the like.

The present invention futher provides a process for the preparation of a pharmaceutical composition comprising a compound of formula (I), which process comprises bringing a compound of formula (I) into association with a pharmaceutically acceptable carrier or excipient.

The compounds of formula (I) are of value in the treatment of a wide variety of clinical conditions which are characterised by the presence of an excess of tachykinin, in particular substance P, activity. These may include disorders of the central nervous system such as anxiety, depression, psychosis and schizophrenia; epilepsy; neurodegenerative disorders such as dementia, including senile dementia of the Alzheimer type, Alzheimer's disease and Down's syndrome; demyelinating diseases such as MS and ALS and other neuropathological disorders such as peripheral neuropathy, including diabetic and chemotherapy-induced neuropathy, and postherpetic and other neuralgias; small cell carcinomas such as small cell lung cancer; respiratory diseases, particularly those associated with excess mucus secretion such as chronic obstructive airways disease, bronchopneumonia, chronic bronchitis, cystic fibrosis and asthma, and bronchospasm; inflammatory diseases such as inflammatory bowel disease, psoriasis, fibrositis, osteoarthritis and rheumatoid arthritis; allergies such as eczema and rhinitis; hypersensitivity disorders such as poison ivy; ophthalmic diseases such as conjunctivitis, vernal conjunctivitis, and the like; cutaneous diseases such as contact dermatitis, atropic dermatitis, urticaria, and other eczematoid dermatitis; addiction disorders such as alcoholism; stress related somatic disorders; reflex sympathetic dystrophy such as shoulder/hand syndrome; dysthymic disorders; adverse immunological reactions such as rejection of transplanted tissues and disorders related to immune enhancement or suppression such as systemic lupus erythematosis; gastrointestinal (GI) disorders and diseases of the GI tract such as disorders associated with the neuronal control of viscera such as ulcerative colitis, Crohn's

disease and incontinence; emesis, including acute, delayed and anticipatory emesis, for example, induced by chemotherapy, radiation, toxins, pregnancy, vestibular disorders, surgery, migraine and variations in intercranial pressure; disorders of bladder function such as bladder detrusor hyper-reflexia; fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis; disorders of blood flow caused by vasodilation and vasospastic diseases such as angina, migraine and Reynaud's disease; and pain or nociception, for example, that attributable to or associated with any of the foregoing conditions, especially the transmission of pain in migraine.

The compounds of formula (I) are particularly useful in the treatment of pain or nociception and/or inflammation and disorders associated therewith such as, for example, neuropathy, such as diabetic and chemotherapy-induced neuropathy, postherpetic and other neuralgias, asthma, osteoarthritis, rheumatoid arthritis and especially migraine.

The present invention further provides a compound of formula (I), or a salt or prodrug thereof, for use in therapy.

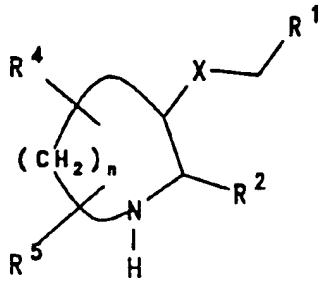
In the treatment of conditions involving actions of tachykinins released physiologically in response to noxious or other stimuli, a suitable dosage level is about 0.001 to 50 mg/kg per day, preferably about 0.005 to 10 mg/kg per day, and especially about 0.005 to 5 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once daily.

According to a further or alternative aspect, the present invention provides a method of treatment of a human or animal subject suffering from or susceptible to

a condition characterised by the presence of an excess of tachykinin which method comprises administering to a human or animal subject in need of such treatment an effective amount of a compound of formula (I), or a salt or prodrug thereof.

The present invention also provides the use of a compound of formula (I), or a salt or prodrug thereof, for the manufacture of a medicament for the treatment of conditions characterised by the presence of an excess of tachykinins.

According to one general process (A), the compounds according to the invention may be prepared by a process which comprises reacting a compound of formula (II):



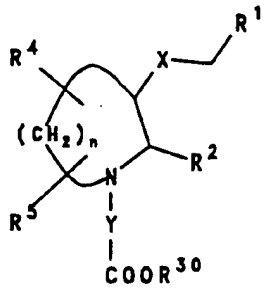
(II)

wherein $R^1$, $R^2$, $R^4$, $R^5$, X and n are as defined for formula (I) above, with a reagent suitable to introduce the group $R^8$, for example, a halide or acyl halide, or corresponding mesylate or tosylate, of formula $R^8$-L, where L represents halo, such as chloro, bromo or iodo, methylsulphonate or p-toluenesulphonate, or any other suitable leaving group, in the presence of a base.

Suitable bases of use in the reaction include inorganic bases such as alkali metal carbonates, for example, potassium carbonate.

Conveniently the reaction is effected in a suitable organic solvent, for example, dimethylformamide.

According to a second process (B), compounds of formula (I) wherein $R^8$ represents $C_{1-6}$alkyl subsituted by $CONR^aC_{1-6}alkylR^{12}$, $CONR^{13}C_{2-6}$alkenyl, $CONR^{13}C_{2-6}$alkynyl, $CONR^aC(NR^b)NR^cR^9$, $CONR^a$heteroaryl or $COR^q$ may be prepared by reaction of an intermediate of formula (III):



(III)

wherein $R^1$, $R^2$, $R^4$, $R^5$, X and n are as defined for formula (I), $R^{30}$ is H or alkyl and Y represents $C_{1-6}$alkylidene with an amine of formula $HNR^aC_{1-6}alkylR^{12}$, $HNR^{13}C_{2-6}$alkenyl, $HNR^{13}C_{2-6}$alkynyl, $HNR^aC(NR^b)NR^cR^9$, $HNR^a$heteroaryl or

in the presence of a base.

Suitable bases of use in the reaction include organic bases such as tertiary amines, for example, triethylamine.

The reaction is preferably effected in the presence of a coupling agent such as, for example, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride.

The reaction is conveniently effected in a suitable organic solvent, such as an ether, for example, tetrahydrofuran, suitably at ambient temperature.

Compounds of formula (I) may also be prepared from different compounds of formula (I) by interconversion processes. In particular, interconversion processes may be used to vary the group $R^8$.

Intermediates of formulae (II) and (III) may be prepared as described in published European patent application no. 0 528 495.

Where the above-described process for the preparation of the compounds according to the invention gives rise to mixtures of stereoisomers these isomers may, if desired, be separated, suitably by conventional techniques such as preparative chromatography.

The novel compounds may be prepared in racemic form, or individual enantiomers may be prepared either by enantiospecific synthesis or by resolution. For example, any suitable intermediates may be resolved into their component enantiomers by standard techniques, such as the formation of diastereomeric esters or amides, followed by chromatographic separation or separation by fractional crystallization and removal of the chiral auxiliary. The diastereomeric intermediates can then be used to prepare optically pure compounds of formula (I).

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in Protective Groups in Organic Chemistry, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene and P.G.M. Wuts, Protective Groups in Organic Synthesis, John Wiley & Sons, 1991. The

protecting groups may be removed at a convenient subsequent stage using methods known from the art.

The following Examples illustrate the preparation of compounds according to the invention.

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DESCRIPTION 1

*cis*-3-((3,5-Bis(trifluoromethyl)phenyl)methyloxy)-2-phenyl piperidine hydrochloride salt

a) A solution of methyl 4-nitrobutyrate (23g) and benzaldehyde (16ml) in acetic acid (39ml) containing ammonium acetate (12.12g) was heated at reflux under nitrogen for 2h. The reaction mixture was cooled to 5°C, whereby a pale-yellow solid crystallised. This was isolated by filtration, then dissolved in dichloromethane, washed cautiously with saturated aqueous sodium bicarbonate solution (2 x), then dried ($MgSO_4$) and concentrated to leave a yellow solid. Recrystallisation from ethyl acetate provided 5-nitro-2-oxo-6-phenylpiperidine (12.5g) as a crystalline, white solid. $^1H$ NMR ($CDCl_3$) δ 7.46-7.26 (m), 6.0 (br s), 5.24 (dd, J = 1.4, 7.0Hz), 4.70 (m), 2.70-2.50 (m), 2.38-2.24 (m).

b) Potassium *t*-butoxide (1.68g) was added to a solution of 5-nitro-2-oxo-6-phenylpiperidine (3g) in a mixture of dichloromethane (50ml) and methanol (50ml) and the mixture was cooled to -78°C under nitrogen. Ozone was bubbled through the solution for 3h. A yellow-green solution resulted, and TLC indicated no starting material remained. The reaction mixture was purged with oxygen for 5 min to remove excess ozone, then dimethylsulfide (7ml) was added and the reaction mixture was allowed to warm to 23°C. The solvent was removed *in vacuo*, and the residue was partitioned between dichloromethane and water. The layers were separated, and the aqueous phase was extracted twice with dichloromethane. The combined organic extracts were washed with brine, then dried ($K_2CO_3$) and concentrated to leave a yellow solid.

This crude material was slurried in dry THF and added to lithium aluminium hydride (1M in THF, 50ml) then heated at

reflux for 12h. After cooling to 23°C, the reaction mixture was quenched by the cautious addition of water (dropwise) under nitrogen, then 2M sodium hydroxide. The mixture was filtered through a pad of Hyflo, the filtrate was washed with brine, then dried ($K_2CO_3$) and concentrated to leave a yellow solid. Purification by silica-gel chromatography ($CH_2Cl_2$/MeOH/$NH_3$ 97:3:1 then $CH_2Cl_2$/MeOH 95:5) provided 3-hydroxy-2-phenylpiperidine as a ca 4:1 mixture of *cis*- and *trans*-isomers respectively. $^1H$ NMR ($CDCl_3$) 7.44-7.20 (m), 3.84 (2), 3.76 (s), 3.54 (m), 3.4 (s), 3.3 (d, J = 8Hz), 3.26 (m), 3.04 (m) 2.78 (ddd, J = 2.9, 11.9, 11.9Hz), 2.70 (ddd, J = 2.9, 11.9, 11.9Hz), 2.18-1.78 (m), 1.48 (m). MS (EI) m/z 177 ($M^+$).

c) Di-*t*-butyldicarbonate (1.36g) was added to a solution of 3-hydroxy-2-phenylpiperidine (1g) in dichloromethane (8ml) under nitrogen and the mixture stirred at 23°C for 3h. The solvent was removed *in vacuo*, and the residue purified by silica-gel chromatography ($CH_2Cl_2$/MeOH/$NH_3$ 97:3:0.5) to provide *cis*- and *trans*-1-*t*-butyloxycarbonyl- 3-hydroxy-2-phenylpiperidine (1.4g) as a clear, viscous oil. $^1H$ NMR ($CDCl_3$) δ 7.50-7.42 (m), 7.40-7.14 (m), 5.36 (d, J = 5.6Hz), 4.50 (m), 4.44 (m), 4.12-3.92 (m), 3.02 (ddd, J = 3.0, 12.5, 12.5Hz), 2.87 (ddd, J = 3.0, 12.5, 12.5Hz), 1.88-1.66 (m), 1.46 (s), 1.36 (s).

d) To a cooled (0°C) solution of 1-*t*-butyloxycarbonyl-3-hydroxy-2-phenylpiperidine (1.4g) in dry dimethylformamide (5ml) was added sodium hydride (80% dispersion in mineral oil; 182mg). The cooling bath was removed and the reaction mixture stirred at 23°C for 30 min. A solution of 3,5-bis(trifluoromethyl) benzyl bromide (1.87g) in dry dimethylformamide (1ml) was added and stirring was continued for 2h at room temperature. The mixture was diluted with water (100ml) and extracted with ethyl acetate (3 x 40ml). The combined organic extracts were

washed with brine (1 x 30ml), dried ($MgSO_4$) and evaporated to yield a pale yellow oil. Purification by chromatography on silica using gradient elution of hexane in ethyl acetate (9:1 - 4:1) afforded the product *cis*-1-*t*-butyloxycarbonyl-3-((3,5-bis (trifluoromethyl)phenyl)methyloxy)- 2-phenylpiperidine (350mg) as a clear viscous oil. $^1H$ NMR (250MHz, $CDCl_3$) δ 7.77 (1H, s, ArH), 7.71 (2H, s, ArH), 7.53-7.57 (2H, m, ArH), 7.2-7.4 (3H, m, ArH), 5.70 (1H, br d, app. J = 7.0Hz, NC<u>H</u>Ph), 4.73 (2H, brs, $OCH_2$), 3.84-3.98 (2H, m, NCHC<u>H</u>O + NC<u>H</u>H), 2.77 (1H, ddd, J=13.0, 13.0, 3.0Hz), NCH<u>H</u>), 2.00 (2H, mc, $CH_2$), 1.6-1.8 (2H, m, $CH_2$), 1.40 (9H, s, $C(CH_3)_3$).

e) Trifluoroacetic acid (3ml) was added to the product of (d) above (800mg) under nitrogen and the resulting solution was stirred for 1h. Excess trifluoroacetic acid was removed *in vacuo* and the residue was partitioned between 2M sodium hydroxide and dichloromethane. The organic phase was washed with brine, dried ($MgSO_4$) and evaporated to afford a colourless oil. Purification on silica (dichloromethane in methanol, 98:2 - 95:5) afforded the product *cis*-3-((3,5-bis(trifluoromethyl)phenyl) methyloxy-2-phenylpiperidine (360mg) as a colourless oil. $^1H$ NMR (360MHz, $CDCl_3$) δ 7.78 (1H, s, ArH), 7.44 (2H, s, ArH), 7.18-7.38 (5H, s, ArH), 4.52 (1H, d, J = 12.5Hz, OC<u>H</u>H), 4.13 (1H, d, J = 12.5Hz, OCH<u>H</u>), 3.84 (1H, d, J = 1.0Hz, NCHPh), 3.68 (1H, d, J = 1.5Hz), 3.28 (1H, m, NCHC<u>H</u>O), 2.84 (1H, ddd, J = 3.0, 12.5, 12.5Hz, NC<u>H</u>H), 2.20 (1H, mc, NCH<u>H</u>), 1.8-1.98 (2H, m, $CH_2$), 1.64-1.78 (1H, m, C<u>H</u>H), 1.50-1.58 (1H, m, CH<u>H</u>); MS m/z 404 $((M+1)^+$, 90%).

The oil was dissolved in ether to which was added excess ethereal hydrogen chloride. Upon standing a white solid crystallised. This was filtered and recrystallised from ethyl acetate-methanol to afford the title compound as white crystals:

mp 200-203°C. $^1$H NMR (360MHz, DMSO) δ 7.95 (1H, s, ArH), 7.81 (2H, s, ArH), 7.37-7.47 (5H, m, ArH), 4.78 (1H, d, J = 13.0Hz, OCHH), 4.56 (1H, s, NCHPh), 4.32 (1H, d, J = 13.0Hz, OCHH), 3.96 (1H, s, NCHCHO), 3.10 (1H, t, J = 13.0Hz, NCHH), 2.23 (1H, d, J = 13.0Hz, NCHH), 1.64-2.00 (4H, m, $CH_2$ x 2); MS ($CI^+$) m/z 404 ($(M+1)^+$, 90%); Found: C, 54.08; H, 4.47; N, 3.13. Calcd. for $C_{20}H_{20}F_6NOCl.0.25H_2O$: C, 54.06; H, 4.65; N, 3.15%.

## DESCRIPTION 2

(2R*,3R*)-3-((3,5-Bis(trifluoromethyl)phenyl)methyloxy)-1-(carbomethoxy)methyl-2-phenylpiperidine

*cis*-3-((3,5-Bis(trifluoromethyl)phenyl)methyloxy)-2-phenyl piperidine hydrochloride (Description 1, 1g) was liberated from the hydrochloride salt by partitioning between ethyl acetate and 2M sodium hydroxide. The organic phase was washed successively with water, saturated brine, dried ($MgSO_4$) and evaporated *in vacuo*. To a solution of the residual oil in tetrahydrofuran (20ml) was added triethylamine (0.4ml) and methyl bromoacetate (400mg) and the solution was heated at reflux under an atmosphere of nitrogen for 16h. To the cooled solution was added ethyl acetate and water and the organic phase washed further with water and dried ($MgSO_4$). After the solvent had been removed *in vacuo* the residue was chromatographed on silica gel eluting with ethyl acetate/petroleum ether (3:10). The product was recrystallised from diethyl ether/petroleum ether to give the title compound, mp =81-83°C. Found: C, 57.35; H, 4.98; N, 2.84; $C_{23}H_{23}F_6NO_3.0.1(H_2O)$ requires C, 57.71; H, 4.86; N, 2.93%. MS ($CI^+$) m/z = 476 $(M+H)^+$.

DESCRIPTION 3

(+)-(2S,3S)-*cis*-3-((3,5-Bis(trifluoromethyl)phenyl)methyloxy)-2-phenylpiperidine hydrochloride salt

a) The mixture of *cis*- and *trans*-isomers of 3-hydroxy-2-phenylpiperidine (Description 1, (2b)) and 4-toluenesulfonic acid monohydrate was crystallized from methanol/ethyl acetate to give *cis*-3-hydroxy-2-phenylpiperidinium tosylate, mp 266-267°C.

b) The tosylate salt (Description 3(a) above) was dissolved in a mixture of ethyl acetate and 10% aqueous $Na_2CO_3$ with warming. The organic phase was washed with saturated brine, dried ($K_2CO_3$) and evaporated to give crystalline *cis*-3-hydroxy-2-phenylpiperidine, mp 110-110.5°C.

c) *cis*-3-Hydroxy-2-phenylpiperidine (Description 3b) and (-)dibenzoyltartrate were dissolved in methanol and crystallized by addition of ethyl acetate. The solid was recrystallised from hot methanol to give the hemi dibenzoyltartrate salt, mp 223-224°C. This was liberated from the salt as described above to give the single enantiomer (+)-*cis*-3-hydroxy-2-phenylpiperidine, mp 93-95°C. $[\alpha]^{23}_D$ = +98.5° (c=1, MeOH). The mother liquors were converted to the free base as described in Description 3b and crystallization using (+)dibenzoyltartrate in an analogous manner to that described above gave (-)-3-hydroxy-2-phenylpiperidine, mp 93-95°C. $[\alpha]^{23}_D$ = -97.2°C (c=1, MeOH).

d) (+)-*cis*-3-Hydroxy-2-phenylpiperidine was reacted according to the procedure detailed in Description 1c-e to give (+)-*cis*-3-((3,5-bis (trifluoromethyl)phenyl)methyloxy)-2-

phenylpiperidine hydrochloride as a crystalline solid: mp 215-216°C. $[\alpha]_D$ = +87.3°C (c=1, MeOH). $^1$H NMR (360MHz, DMSO-$d_6$) δ 7.95 (1H, s, ArH), 7.81 (1H, s, ArH), 7.47 (2H, m, ArH), 7.37 (3H, m, ArH), 4.78 (1H, d, J = 13.0Hz, OCHH), 4.56 (1H, s, NCHPh), 4.32 (1H, d, J = 13.0Hz, OCHH), 3.96 (1H, s, NCHCHO), 3.10 (1H, t, J = 13.0Hz, NCHH), 2.23 (1H, d, J = 13.0Hz, NCHH), 2.00-1.64 (4H, m, $CH_2$ x 2); MS ($CI^+$) m/z 404 ($M+1^+$, 90%); Found: C, 54.52; H, 4.60; N, 3.11. Calcd. for $C_{20}H_{19}F_6NO.HCl$: C, 54.62; H, 4.58; N, 3.18%.

## DESCRIPTION 4

(+)-(2S,3S)-3-((3,5-Bis(trifluoromethyl)phenyl)methyloxy)-1- (carbomethoxy)methyl-2-phenylpiperidine

The title compound was prepared from (+)-*cis*-3-((3,5-bis (trifluoromethyl)phenyl)methyloxy)-2-phenylpiperidine (Description 3) using the procedure detailed in Description 2: mp 60-70°C. $[\alpha]_D$ = +132.3° (c=1, MeOH). $^1$H NMR (360MHz, $CDCl_3$) δ 1.57-1.63 (3H, m, $CH_2$ + CHH), 2.04-2.17 (2H, m, CHH, CHHN), 3.07-3.10 (1H, m, NCHCHO), 3.20 (1H, d, J = 17.0Hz, NCHH$CO_2CH_3$), 3.31 (1H, d, J = 17.0Hz, NCHCH $CO_2CH_3$), 3.58 (3H, s, $CH_3$), 3.93 (1H, s, NCHPh), 4.07 (1H, d, J = 12.0Hz, OCHH), 4.49 (1H, d, J = 12.0Hz, OCHH), 7.28-7.34 (3H, m, ArH), 7.43-7.45 (2H, m, ArH), 7.54 (2H, s, ArH), 7.71 (1H, s, ArH). MS ($CI^+$) m/z 476 ($M+1^+$, 100%). Found: C, 58.31; H, 4.90; N, 2.94. Calcd. for $C_{23}H_{23}F_6NO_3$: 58.11; H, 4.88; N, 2.95%.

## DESCRIPTION 5

(2R*,3R*)-3-((3,5-Bis(trifluoromethyl) phenyl)methyloxy)-1-(carboxymethyl)-2-phenylpiperidine.

The ester of Description 2 (4.98g) was dissolved in anhydrous THF (80ml) and an aqueous solution of potassium hydroxide (1.76g). The reaction was brought to reflux for 3 hrs and allowed to cool. The THF was removed *in vacuo* and the residue freeze dried, this afforded a yellow solid, which was dissolved in the minimum amount of water and the pH adjusted to 6.0 by careful addition of 1M HCl. A white precipitate was formed, this was filtered, re-dissolved in ethyl acetate and dried ($MgSO_4$). The solvent was removed *in vacuo* to afford a yellow solid (4.59g). The product was recrystallised from ethyl acetate/petrol as the zwitterion: mp 172-175°C. $^1H$ NMR (360MHz, DMSO) δ 1.44-1.60 (2H, m, C<u>H</u>$_2$), 1.82-1.97 (1H, m, C<u>H</u>H), 2.12-2.24 (1H, m, C<u>H</u>H), 2.46-2.63(1H, m, C<u>H</u>H), 2.80 (1H, d, J =17.0Hz, NCHH) 3.02-3.06 (1H, m, C<u>H</u>H) 3.12 (1H, d, J=17.0Hz, NCH<u>H</u>), 3.57 (1H, s, C<u>H</u>O), 3.80 (1H, m, NC<u>H</u>Ph), 4.09 (1H, d, J = 13Hz, OC<u>H</u>H), 4.63 (1H, d, J = 13Hz, OCH<u>H</u>), 7.22-7.40 (5H, m, Ar-H), 7.70 (2H, s, Ar<u>H</u>), 7.93 (1H, s, Ar<u>H</u>); MS($CI^+$) m/z 462 ($M^+$+1, 30%); Found: C, 57.33 ; H, 4.59 ; N, 3.14. Calcd. for $C_{22}H_{21}F_6NO_3$: C, 57.26 ; H, 4.59 ; N, 3.04.

## DESCRIPTION 6

(2S,3S)-3-((3,5-Bis(trifluoromethyl)phenyl)methyloxy)-1-(carboxymethyl)-2-phenylpiperidine

The title compound was prepared from the compound of Description 4 using the procedure detailed in Description 5: MS($CI^+$) m/z 462 ($M^+$+1).

## EXAMPLE 1

(2R*,3R*)-3-((3,5-Bis(trifluoromethyl)phenyl)methyloxy)-2-phenyl-1- (N-(prop-2-ynyl)carboxamidomethyl)piperidine

The product of Description 5 (1g) was dissolved in anhydrous THF (40ml) under nitrogen. 1-Hydroxybenzotriazole

hydrate (1.2g), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.66g), triethylamine (1.2ml) and propargylamine (0.55ml) were added and the reaction was allowed to stir overnight at room temperature. The solvent was removed *in vacuo* and the residual yellow oil dispersed between water and ethyl acetate. The organic layer was washed with 1M citric acid, water, sodium hydrogen carbonate, brine, dried ($MgSO_4$) and concentrated *in vacuo* to afford a yellow oil. This was purified on silica using 50% ethyl acetate in petrol as eluant. The product was purified further by medium pressure chromatography eluting with 30% ethyl acetate in petrol to afford the title compound as a colourless oil. $^1H$ NMR (360 MHz, DMSO) δ 1.54-1.68 ( 2H, m, C<u>H</u>$_2$), 2.00-2.34 (4H, m, NCH<u>H</u>C<u>H</u>$_2$ + NHCH$_2$C=C<u>H</u>), 2.55 (1H, d, J = 16Hz, NC<u>H</u>HCONH), 3.07 (1H, bd, NC<u>H</u>H), 3.20 (1H, d, J = 16 Hz,. NC<u>H</u>HCONH), 3.45 (1H, m, C<u>H</u>O), 3.59 (1H, m, C<u>H</u>Ph), 4.00-4.18 (3H, m, OC<u>H</u>H + NHC<u>H</u>$_2$CCH), 4.48 (1H, d, J = 12Hz, OC<u>H</u>H), 7.13-7.40 (6H, m, ArH+N<u>H</u>), 7.55 ( 2H, s, ArH). 7.74 (H, s, ArH) ; MS ($CI^+$) 497 ($M+1^+$, 20%); Found: C, 59.81; H, 4.81; N, 5.54. Calcd. for $C_{25}H_{24}N_2O_2F_6$: C, 60.20 ; H, 4.85 ; N, 5.62%.

<u>EXAMPLE 2</u>

<u>(2R*,3R*)-3-((3,5-Bis(trifluoromethyl)phenyl)methyloxy)-1-(N- furfurylcarboxamidomethyl)-2-phenylpiperidine</u>

Following the method of Example 1, the product of Description 5 was reacted with furfurylamine to afford the title compound: mp 80-83°C. Found: C, 59.83; H, 4.84; N, 5.32; Calcd. for $C_{27}H_{27}F_6N_3O_3$: C, 59.99; H, 4.85; N, 5.18%

<u>EXAMPLE 3</u>

<u>(2R*,3R*)3-((3,5-Bis(trifluoromethyl)phenyl)methyloxy)-2-phenyl-1- (N-(3-pyridylmethyl)carboxamidomethyl)piperidine.</u>

Following the method of Example 1, the product of Description 5 was reacted with 3-(aminomethyl) pyridine to give the title compound: mp 127-130°C. Found: C, 60.75; H, 5.05; N, 7.34; Calcd. for $C_{28}H_{27}F_6N_3O_2$: C, 60.98; H, 4.93; N, 7.62%

EXAMPLE 4

(2R*,3R* )-3-((3,5-Bis(trifluoromethyl)phenyl)methyloxy)-1- (N-(2-methoxyethyl)carboxamidomethyl)-2-phenylpiperidinium hydrochloride

Following the method of Example 1, the product of Description 5 was reacted with 2-methoxyethylamine to give the title compound after treatment with ethereal HCl: mp 146-148°C. Found: C, 53.85; H, 5.37; N, 4.79; Calcd. for $C_{25}H_{28}F_6N_3O_3$ HCl: C, 54.11; H, 5.27; N, 5.05%.

EXAMPLE 5

(2R*,3R*)-3-((3,5-Bis(trifluoromethyl)phenyl)methyloxy)-1-(carboxyhydrazidomethyl)-2-phenylpiperidinium hydrochloride

Hydrazine hydrate (3.0ml) was added to a solution of the compound of Description 2 (2.95g) in ethanol (80ml). The solution was heated to reflux for 18h after which the ethanol was removed *in vacuo*. The residue was extracted into ethyl acetate and the organic layer was washed with brine, dried ($MgSO_4$) and concentrated to give the title compound (2.79g). This was dissolved in methanol (5ml) and a methanolic solution of hydrogen chloride was added. Methanol was removed *in vacuo* and the salt was recrystallised from diethyl ether to give the hydrochloride salt. $^1$H NMR (360MHz, DMSO) δ 1.77-1.93 (2H, m, $CH_2$), 2.08-2.21 (1H, m, $CH_2$), 2.22-2.35 (1H, m, $CH_2$), 3.56 (1H, d, NC<u>H</u>HCH$_2$), 3.64 (1H, d, J = 16.5Hz, NC<u>H</u>HCO), 3.77 (1H, d, NCH<u>H</u>CH$_2$), 3.92 (1H, d, J = 16.5Hz, NCH<u>H</u>CO), 3.96 (1H, brs, C<u>H</u>O), 4.37 (1H, d, J = 13.0Hz, OC<u>H</u>H), 4.83 (1H, d, J=13.0Hz, OCH<u>H</u>), 4.95 (1H, s, CHPh), 7.36-7.46 (3H, m, ArH),

7.53-7.62 (2H, brs, ArH), 7.95 (2H, s, ArH), 7.97 (1H, s, ArH); MS $(CI)^+$ m/z 475.

EXAMPLE 6

(2S,3S)-1-(N-Amidino(carboxamidomethyl))-3-((3,5-bis (trifluoromethyl)phenyl)methyloxy-2-phenylpiperidine

Guanidine hydrochloride (600mg) was added to a solution of sodium (150mg) in methanol (30ml) and the solution was heated at reflux for 30 min. To this solution was added the ester of Description 4 and the resulting solution was heated at reflux for 1h. The solution was cooled, and concentrated *in vacuo*. The residue was dispersed between ethyl acetate and water. The organic phase was separated, dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on alumina (grade III) using a gradient elution of 1-10% methanol in dichloromethane. This afforded the desired product which was recrystallised from ether/hexane: mp 159-160°C. Found: C, 54.77; H, 4.99; N, 11.19. Calcd. for $C_{23}H_{24}F_6N_4O_2$: C, 54.98; H, 4.81; N, 11.15%.

EXAMPLE 7

(2S,3S)-3-((3,5-Bis(trifluoromethyl)phenyl)methyloxy)-2-phenyl-1-(N-methyl-N-(3-pyridylmethyl)carboxamidomethyl) piperidinium hydrobromide

(a) (N-(Chloroacetyl)-N-methylaminomethyl)pyridinium hydrochloride

Chloroacetyl chloride (790mg) was added dropwise to a chilled solution of 3-(N-methylaminomethyl)pyridine in dichloromethane (30ml). The resulting solution was stirred at 5°C for 2h. Removal of solvent afforded the product as a white crystalline solid: mp 120-121°C. $^1H$ (360MHz DMSO-$d_6$) 3.1 (3H, s, NMe), 4.50 (2H, s, $ClCH_2CO$), 4.75 (2H, s,

N-C$\underline{H}_2$-pyridine), 8.01 (1H, dd, J=6.0, 5.5Hz, ArH), 8.43 (1H, m, ArH), 8.89 (2H, m, ArH); MS m/z ($CI^+$) 199 ($M^+$+1).

(b) (2S,3S)-3-((3,5-Bis(trifluoromethyl)phenyl)methyloxy)-2-phenyl-1-(N-methyl-N-(3-pyridylmethyl)carboxamidomethyl) piperidine dihydrobromide

Diisopropylethylamine (4.3ml) was added to a stirred suspension of 3-(N-(chloracetyl)-N-methylaminomethyl)pyridine hydrochloride (1.6g) and the compound of Description 3 (3.6g). The resulting solution was stirred at room temperature for 18h. After this time the white precipitate was filtered off and the solvent removed under reduced pressure. The solid residue was taken up in water (50ml) and extracted into ethyl acetate (2x50ml). The organic extracts were combined, dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The product was isolated by flash chromatography on silica gel using 20% ethyl acetate in hexane as eluent. The isolated free base was treated with a solution of hydrogen bromide in ether, followed by recrystallisation from methyl-*t*-butyl ether to afford the product as an amorphous solid: mp 68-70°C. $^1H$ NMR (360MHz, $CDCl_3$, free base), 1.6 (2H, m, C$\underline{H}_2$C$H_2$N), 2.1 (2H, m, C$\underline{H}_2$C$H_2$), 2.68 (3H, s, NC$\underline{H}_3$), 2.79 (2H, s, $CH_3$N-C$\underline{H}_2$), 3.15 (2H, m, C$\underline{H}_2$ NCH), 3.59 (1H, bs, NC$\underline{H}$-Ph), 4.08 (2H, m, C$\underline{H}$-O-$CH_2$Ar and C$\underline{H}$H-CO), 4.3 (1H, d, J=10.0Hz, OC$\underline{H}$H-Ar), 4.60 (2H, m, CH$\underline{H}$CO and OCH$\underline{H}$-Ar), 7.1-7.25 (7H, m, Ar-H), 7.51 (2H, s, ArH), 7.63 (1H, s, ArH), 8.15-8.3 (2H, m, Ar-H): MS m/z ($CI^+$) 567 ($M^+$+1). Found: C, 46.63; H, 4.64; N, 5.46. Calcd. for $C_{29}H_{29}F_6N_3O_2$. 2HBr.$\underline{H}_2$O: C, 46.72; H, 4.46; N, 5.63%.

EXAMPLE 8

(2S,3S)-3-((3,5-Bis(trifluoromethyl)phenyl)methyloxy)-1-(2-morpholino-2-oxo)ethyl-2-phenylpiperidinium hydrochloride

The compound of Description 6 (2g), triethylamine (2.42ml), morpholine (1.5ml), hydroxybenzotriazole (2.35g) and 1-(3-dimethylaminopropyl)-3-ethylcarbodimide hydrochloride (1.66g) were suspended in dimethylformamide (25ml) and the reaction mixutre was allowed to stir under nitrogen for 12h. The solvent was removed *in vacuo* and the residual yellow oil was dispersed between water and ethyl acetate. The organic layer was washed successively with 1M citric acid, water, sodium hydrogen carbonate solution, brine, then dried ($MgSO_4$) and concentrated *in vacuo* to afford a yellow oil. This was purified by chromatography on silica using 70% ethyl acetate in petrol as eluent. This afforded the title compound as a colourless oil. Treatment of this oil with ethereal hydrogen chloride afforded the hydrochloride salt which was recrystallised from ethyl acetate/petrol: mp 90-91°C. $^1$H NMR (360MHz, DMSO-$d_6$) δ 1.49-1.52 (2H, m, $CH_2$), 1.89-1.90 (1H, m, $CH_2$), 2.12-2.18 (1H, m, $CH_2$), 2.41-2.47 (1H, m, C<u>H</u>HN), 2.76 (1H, d, J=15.0Hz, NC<u>H</u>HCO), 2.96-2.99 (1H, m, CH<u>H</u>N), 3.16 (1H, d, J=15.0Hz, NCH<u>H</u>CO), 3.29-3.32 (2H, m, $CH_2$-morpholine), 3.43-3.48 (6H, m, $CH_2$-morpholine), 3.57 (1H, s, C<u>H</u>O), 3.61 (1H, s, NC<u>H</u>Ph), 4.15 (1H, d, J=13.0Hz, OC<u>H</u>H), 4.65 (1H, d, J=13.0Hz, OCH<u>H</u>), 7.24-7.28 (3H, m, ArH), 7.39-7.41 (2H, m, ArH), 7.76 (2H, s, ArH), 7.94 (1H, s, ArH); MS ($CI^+$) m/z 530 ($(M+1)^+$, 70%). Found: C, 53.82; H, 5.35; N, 4.90; Cl, 6.20; Calcd. for $C_{26}H_{28}F_6N_2O_3.HCl.H_2O$: C, 53.38; H, 5.34; N, 4.79; Cl, 6.06%.

EXAMPLE 9

(2S,3S)-3-((3,5-Bis(trifluoromethyl)phenyl)methyloxy)-1-(2-oxo-2-piperidino)ethyl-2-phenylpiperidinium hydrochloride

The title compound was prepared following the method described in Example 8, using piperidine as a starting material; this afforded a white crystalline material: mp 89-91°C. $^1$H NMR (360MHz, DMSO-$d_6$) δ 0.85-0.92 (1H, m, CHH), 1.08-1.14 (1H, m, CHH), 1.25-1.34 (2H, m, $CH_2$), 1.38-1.46 (2H, m, $CH_2$), 1.76-1.88 (2H, m, $CH_2$), 2.20-2.32 (2H, m, $CH_2$), 2.49-2.51 (4H, m, 2x$CH_2$), 3.16-3.24 (1H, m, CHHN), 3.40-3.48 (1H, m, CHHN), 3.82 (1H, d, J=17.0Hz, N-CHHCO), 3.93 (1H, d, J=17.0Hz, N-CHHCO), 3.98 (1H, s, CHO), 4.43 (1H, d, J=13.0Hz, OCHH), 4.86 (1H, d, J=13.0Hz, OCHH), 5.07 (1H, s, NCHPh), 7.24-7.27 (3H, m, ArH), 7.41-7.44 (2H, m, ArH), 7.80 (2H, s, ArH), 7.95 (1H, s, ArH); MS ($Cl^+$) m/z 529 ($(M+1)^+$, 100%).

EXAMPLE 10

(2S,3S)-3-((3,5-Bis(trifluoromethyl)phenyl)methyloxy)-1-(2-oxo-2-(4-methylpiperazinyl))ethyl-2-phenylpiperidinium hydrochloride

The title compound was prepared following the method described in Example 8 using N-methylpiperazine as a starting material; this afforded the product as a white powder. $^1$H NMR (360MHz, DMSO-$d_6$) δ 1.48-1.52 (2H, m, $CH_2$), 1.8-1.90 (1H, m, CHH), 2.18-2.24 (1H, m, $CH_2$), 2.38-2.44 (1H, m, NCHH), 2.50 (3H, s, $CH_3$), 2.71 (1H, d, J=14.0Hz, CHHCO), 2.94-2.97 (1H, m, NCHH), 3.15 (1H, d, J=14.0Hz, CHHCO), 3.20-3.25 (2H, m, CHO), 3.25-3.31 (4H, m, $NCH_2CH_2N$), 3.42-3.57 (4H, m, $NCH_2CH_2N$), 4.15 (1H, d, J=13.0Hz, OCHH), 4.65 (1H, d,

J=13.0Hz, OCHH), 7.24-7.26 (3H, m, ArH), 7.39-7.42 (2H, m, ArH), 7.76 (2H, s, ArH), 7.95 (1H, s, ArH); MS ($CI^+$) m/z 543 ($(M+1)^+$, 80%).

## EXAMPLE 11

(2R*, 3R*)-3-Benzyloxy-1-(2-morpholino-2-oxo)ethyl-2-phenylpiperidinium hydrochloride

(a) Bromoacetylmorpholine

Bromoacetylbromide (20.1g) was added dropwise to a rapidly stirred solution of morpholine (17.4g) in ether (200ml). After stirring overnight, the mixture was washed with water (2 x 50ml), dried ($MgSO_4$) and evaporated to afford a colourless oil. $^1H$ NMR (360MHz, $CDCl_3$) δ 3.46 (2H, m, 2 x CHHN), 3.63 (2H, m, 2 x CHHN), 3.69 (4H, m, 2 x $CH_2O$), 3.75 (2H, s, $CH_2Br$).

(b) (2R*, 3R*)-3 Benzyloxy-1-(2-morpholino-2-oxo)ethyl-2-phenylpiperidinium hydrochloride

A mixture of the compound of Description 1 (139mg), bromoacetylmorpholine (208mg) and potassium carbonate (50mg) in dimethylformamide (10ml) was heated to 100°C under $N_2$ for 5h. The mixture was cooled, diluted with water (50ml) and extracted with ethyl acetate (2 x 50ml). The combined extracts were washed with brine (50ml), dried ($MgSO_4$) and evaporated to afford a yellow oil. This was purified by column chromatography on silica eluting with ethyl acetate to afford a colourless oil. Formation of the hydrochloride salt and recrystallisation from ethyl acetate/hexane afforded the title compound; mp 84-85°C.

EXAMPLE 12

(2R*,3R*)-3-((3,5-Bis(trifluoromethyl)phenyl)methyloxy)-2-phenyl-1-(thiocarboxamidomethyl)piperidine

(a) (2R*,3R*)-3-((3,5-Bis(trifluoromethyl)phenyl)methyloxy)-1-(cyanomethyl)-2-phenylpiperidinium hydrochloride

The compound of Description 1 (5g), potassium carbonate (1.7g) and bromoacetonitrile (0.87ml) were suspended in dimethylformamide (15ml) and the mixture was stirred under nitrogen at 60°C for 3h. The mixture was cooled, diluted with water (200ml) and extracted with ethyl acetate (2 x 50ml). The organic extracts were washed with brine, dried ($MgSO_4$) and evaporated, affording a brown oil. This was purified on silica using ethyl acetate in petrol (10%) as eluant. This afforded the product as a colourless oil. The hydrochloride salt was prepared by dissolution in ethereal hydrogen chloride and the salt was recrystallised from ether-hexane: mp 133-134°C. $^1H$ NMR (360MHz, $CDCl_3$) δ 1.75 (2H, mc, CHH), 1.90 (2H, mc, CHH), 2.31 (1H, mc, CHH), 2.71 (1H, mc, CHH), 3.19 (1H, mc, CHHN), 3.72 (1H, mc, CHHN), 3.81 (1H, d, J = 17.5Hz, NCHHCN), 3.86 (1H, s, CHO), 4.02 (1H, d, J = 17.5Hz, NCHHCN), 4.09 (1H, s, CHPh), 4.35 (1H, d, J = 13.0Hz, OCHH), 4.73 (1H, d, J = 13.0Hz, OCHH), 7.4 (3H, mc, ArH), 7.69-7.73 (5H, m, ArH); MS ($CI^+$) m/z 443 ($M^+$+1, 30%). Found: C, 54.87; H, 4.30; N, 5.66. Calcd. for $C_{22}H_{18}F_6N_2O.HCl$: C, 55.18; H, 4.42; N, 5.85%.

(b) (2R*,3R*)-3-((3,5-Bis(trifluoromethyl)phenyl) methyloxy)-2- phenyl-1-(thiocarboxamidomethyl)piperidine

The compound of (b) above (1g) was dissolved in dimethylformamide (anhydrous, 10ml) and the solution was

saturated with dry hydrogen chloride gas. The reaction was heated to 100°C under nitrogen and thioacetamide (0.34g) was added; this mixture was allowed to stir at 100°C for 3h. Dimethylformamide was removed *in vacuo*. The residue was extracted with ethyl acetate and the organic layer was washed with aqueous sodium bicarbonate, brine, dried ($MgSO_4$) and concentrated *in vacuo* to afford a brown oil. This was purified on silica using a gradient elution of ethyl acetate in petrol (10-50%). The product was further purified by recrystallisation from ethyl acetate-petrol; mp 164-166°C. $^1H$ NMR (360MHz, $CDCl_3$) δ 1.56-1.70 (2H, m, $CH_2$), 1.96-2.10 (1H, m, CHH), 2.15-2.32 (2H, m, CHHN + CHH), 2.98-3.06 (1H, bd, NCHH), 3.09 (1H, d, J = 18.0Hz, CHHSNH$_2$), 3.50 (1H, d, J = 18.0Hz, NCHHCSNH$_2$), 3.50 (1H, s, CHO), 3.60 (1H, s, NCHPh), 4.04 (1H, d, J = 12.0Hz, OCHHAr), 4.47 (1H, d, J = 12.0Hz, OCHHAr), 7.26-7.36 (5H, m, CHPh), 7.53 (2H, s, Ar-H), 7.75 (H, s, Ar-H), 7.61 (1H, bs, NHH), 8.99 (1H, bs, NHH); MS ($CI^+$) m/z 477 ($M^+$+1, 15%); Found: C, 55.09; H, 4.58; N, 5.97. Calcd. for $C_{22}H_{22}F_6N_2OS$: C, 55.46; H, 4.65; N, 5.88.

## EXAMPLE 13

(2S, 3S)-3-((3,5-Bis(trifluoromethyl)phenyl)methyloxy)-2-phenyl-1-(N-(2-pyridylmethyl)carboxamidomethyl)piperidine

The compound of Description 6 was reacted with 2-(aminomethyl)pyridine to afford the title compound: mp 112-114°C. Found: C, 61.27; H, 5.12; N, 7.59. Calcd. for $C_{28}H_{27}F_6N_3O_2$: C, 60.98; H, 4.93; N, 7.62%. MS ($CI^+$) m/z 552 ($M^+$ +1, 30%).

EXAMPLE 14

2-[(2S, 3S)-3-((3,5-Bis(trifluoromethyl)phenyl)methyloxy)-2-(diphenylmethyl)pyrrolidinol-N-(carbomethoxy)acetamidrazone

(a) N-Carbomethoxy-2-chloroacetamidrazone

Sodium methoxide (0.032g) was added to a solution of chloroacetonitrile (1.26ml) in anhydrous methanol (15ml) at 0°C. The reaction mixture was stirred at room temperature for 0.5h and then neutralised with acetic acid (0.034ml). Methyl hydrazinocarboxylate (1.79g) was added and the reaction mixture stirred at room temperature for 0.5h. The solution was concentrated *in vacuo* to give the title compound as a white solid; mp 138-140°C. MS $(CI)^+$ m/z 166.

(b) (2S,3S)-3-((3,5-Bis(trifluoromethyl)phenyl) methyloxy)-2-(diphenylmethyl)pyrrolidinium hydrochloride

(i) N-*t*-Butyloxycarbonyl-(S)-diphenylalanal

A solution of methyl sulfoxide (4.4ml) in dichloromethane (13ml) was added dropwise to a cooled (-78°C) solution of oxalyl chloride (4ml) in dichloromethane (50ml). After 15 min, a solution of N-*t*-butyloxycarbonyl-(S)-diphenylalanol (10g) in dichloromethane (150ml) was added dropwise at -30°C. The solution was allowed to stir for 30 min, triethylamine (17ml) was added and the solution was allowed to warm to -10°C. Ice-water (200ml) was added to the solution which was then poured onto hexane (600ml). The organic phase was separated, washed successively with citric acid (200ml), saturated aqueous sodium bicarbonate (2 x 150ml), brine (1 x 150ml) then dried ($MgSO_4$) and concentrated *in vacuo* to leave a white crystalline solid. $^1H$ NMR (250MHz, $CDCl_3$) δ 1.42 (9H, s,

$C(CH_3)_3$), 4.48 (1H, d), 4.86 (1H, d), 5.10 (1H, t), 7.26 (10H, m, ArH), 9.6 (1H, s, CHO).

(ii) N-*t*-Butyloxycarbonyl-1-(diphenylmethyl)-2-hydroxy-pent-4-enyl-1-amine

A solution of N-*t*-butyloxycarbonyl-(S)-diphenylalanal (10.9g) in tetrahydrofuran (60ml) was added dropwise to a soluton of allyl magnesium chloride (2M in tetrahydrofuran, 36ml) at -10°C. After 30 min the mixture was poured onto ice-cold saturated aqueous ammonium chloride and the resulting mixture was extracted with ethyl acetate (3 x 150ml). The combined organic extracts were washed with brine (1 x 100ml), then dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography on silica gel using hexane in ethyl acetate (gradient elution of 9:1 to 4:1) as eluant to afford the compound as a white solid. $^1H$ NMR (360MHz, $CDCl_3$) δ 1.42 (9H, s, $(CH_3)_3$), 2.22 (2H, m), 2.68 (3H, brs), 3.48 (t), 3.57 (1H, m), 3.86 (1H, s), 4.07 (d, J = 11Hz), 5.04 (1H, m), 5.71 (1H, m), 6.97-7.36 (10H, m, ArH).

(iii) 2-((3,5-Bis(trifluoromethyl)phenyl)methyloxy)-N-*t*-butyloxycarbonyl-1-(diphenylmethyl)-pent-4-enyl-1-amine

Sodium hydride (80% in oil, 0.53g) was added to a solution of 3,5-bis(trifluoromethyl)benzyl bromide (5ml) and the compound of (13b) above (5g) in dimethylformamide (8ml). After stirring for 1h water (80ml) was added and the mixture was extracted with ethyl acetate (3 x 100ml). The combined organic extracts were washed with brine (1 x 100ml) then dried ($MgSO_4$) and concentrated to leave an oil which was purified on silica using hexane in ethyl acetate as eluant (gradient elution of 97:3 to 4:1). This afforded the title compound as a colourless oil. $^1H$ NMR (360MHz, $CDCl_3$) δ 1.25 (s), 1.30 (s), 2.35 (m), 3.31 (m),

3.40 (dd, J = 5.2, 8.3Hz), 3.97 (d), 4.27 (d), 4.38 (m), 4.65 (m), 4.85 (d), 5.16-5.02 (m), 5.77 (m), 7.35-7.13 (m), 7.76 (s), 7.85 (s).

(iv) (2S,3S)-3-((3,5-Bis(trifluoromethyl)phenyl) methyloxy-2-(diphenylmethyl)pyrrolidinium hydrochloride

A solution of the compound of (c) above (5.2g) in dichloromethane (40ml) and methanol (40ml) was treated with a stream of ozone in oxygen at -78°C for 1h. Methyl sulfide (3ml) was added and the mixture was warmed to 23°C and concentrated *in vacuo*. The residue was dissolved in chloroform (50ml), triethylsilane (5.6ml) was added followed by dropwise addition of a solution of trifluoroacetic acid (6.9ml) in chloroform (5ml). After 1h the solvent was evaporated *in vacuo* and trifluoroacetic acid (10ml) was added to the residue. After stirring for 30 min the mixture was concentrated *in vacuo* and the residue was partitioned between dichloromethane and saturated aqueous sodium bicarbonate. The organic layer was dried ($K_2CO_3$) and concentrated to leave a brown oil. This was purified on silica gel eluting with dichloromethane/methanol (99:1) to provide the title compound as the free base. This was converted to the salt by treatment with methanolic hydrogen chloride: mp >230°C. $[\alpha]^{23}_D$ = +46.6°C (c=1, $CH_3OH$). Found: C, 59.95; H, 4.74; N, 2.63%. Calcd. for $C_{26}H_{23}F_6NO.HCl.0.2H_2O$: C, 60.11; H, 4.73; N, 2.70%.

(c) The compound of (b) above (155mg) was stirred with N-carbomethoxy-2-chloroacetamidrazone (a) (0.3g) in dimethylformamide (5ml) in the presence of potassium carbonate (260mg) at 70°C for 14h. After cooling, the material was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried ($MgSO_4$) and filtered. The solvent was evaporated and the residue was purified by chromatography on silica using 5% methanol in ethyl acetate as eluant. $^1H$ NMR (360MHz, $CDCl_3$) δ 1.93 (2H, m), 2.60 (1H, m), 2.68 (1H, d,

J=14Hz), 2.96 (1H, d, J=14Hz), 3.16 (1H, m), 3.70 (1H, m), 3.74 (3H, s), 4.09 (1H, m), 4.28 (2H, m), 4.66 (1H, brs), 7.35-7.11 (10H, m), 7.52 (2H, s), 7.77 (1H, s).

## EXAMPLE 15

(2S, 3S)-3-(3,5-Bis(trifluoromethyl)phenyl)methyloxy-1-bis(carbomethoxy)methyl-2-phenylpiperidine

The compound of Description 3 (0.439g) was dissolved in dimethylformamide (3ml) and dimethyl bromomalonate (0.274g) and potassium carbonate were added. The mixture was heated at 60°C overnight. The mixture was diluted with water and extracted into ethyl acetate. The organic phase was washed with water, dried ($MgSO_4$) and evaporated. The residue was purified by chromatography on silica using gradient elution of 5-20% ethyl acetate in hexane. This afforded the product as a clear oil. $^1H$ NMR (360MHz, $CDCl_3$) δ 1.55-161 (2H, m), 2.04-2.17 (2H, m), 2.68-2.74 (1H, m), 3.37-3.41 (1H, m), 3.53 (1H, brs), 3.67 (3H, s, $CH_3$), 3.71 (3H, s, $CH_3$), 3.97 (1H, d, J=2Hz), 4.02 (1H, d, J=12.5Hz, OCHH), 4.26 (1H, s), 4.44 (1H, d, J=12.5Hz, OCHH), 7.25-7.34 (3H, m, ArH), 7.40-7.42 (2H, m, ArH), 7.51 (2H, s, ArH), 7.71 (1H, s, ArH).

## EXAMPLE 16

(2S, 3S)-3-(3,5-Bis(trifluoromethyl)phenyl)methyloxy)-1-bis(carboxamido)methyl-2-phenylpiperidinium hydrochloride

(a) 2-Bromomalonamide

2-Cyanoacetamide (5g) was dissolved in glacial acetic acid (50ml) and stirred under nitrogen. Bromine (9.5g) was dissolved

in acetic acid and added dropwise to the solution; after 2h the mixture was evaporated to afford a white slurry. The title compound was recrystallised from ethanol. MS ($CI^+$) m/z 181 ($M+1^+$, 20%).

(b) (2S, 3S)-3-(3,5-Bis(trifluoromethyl)phenyl)methyloxy)-1-bis(carboxamido)methyl-2-phenylpiperidinium hydrochloride

The compound of Description 3 (0.65g) was dissolved in dimethylformamide (5ml) under nitrogen and potassium carbonate (0.199g) and 2-bromomalonamide (0.35g) were added. The reaction mixture was stirred at 60°C for 3h. The compound was isolated following the procedure described in Example 15 and was purified by chromatography on silica using 4% methanol in dichloromethane as eluant to afford a white solid.

Treatment with ethereal hydrogen chloride afforded the title compound: mp 189-194°C. $^1H$ NMR (360MHz, $CDCl_3$) δ 1.56-1.74 (2H, m, $NCH_2CH_2C\underline{H}_2$), 1.94-2.10 (1H, m, $NCH_2C\underline{H}H$), 2.15-2.24 (1H, m, $NCH_2CH\underline{H}$), 2.75-2.86 (1H, m, $NC\underline{H}H$), 2.97-3.07 (1H, m, $NCH\underline{H}$), 3.60 (H, bs, $C\underline{H}O$, 3.85 (1H, bs, $NC\underline{H}Ph$), 4.13 (1H, d, J=12Hz, $OC\underline{H}HAr$), 4.50-4.60 (2H, m, $NC\underline{H}(CONH_2)_2$ + $OCH\underline{H}Ar$), 5.44 (1H, bs, $N\underline{H}$), 5.71 (1H, bs, $N\underline{H}$), 7.27-7.37 (3H, m, ArH), 4.43-7.50 (2H, m, $Ar\underline{H}$), 7.62 (2H, s, ortho H's), 7.76 (1H, s, para H's), 8.01-8.25 (2H, m, $N\underline{H}$+$N\underline{H}$). MS ($CI^+$) m/z 504 ($M+1^+$, 30%). $C_{23}H_{23}N_3O_3F_6$. HCl. requires C, 51.17; H, 4.48; N, 7.78. Found: C, 51.00; H, 4.27; N, 7.67.

EXAMPLE 17

(2S, 3S)-3-(3,5-Bis(trifluoromethyl)phenyl)methyloxy)-1-(N-methanesulfonyl)carboxamidomethyl)-2-phenylpiperidine

(a) N-Bromoacetylmethanesulfonamide

Sodium hydride (1.68g x 60%) was added to a stirred solution of methanesulfonamide (2.0g) in dry tetrahydrofuran (20ml) at room temperature. The resulting solution was stirred at room temperature for 1h, at which time it was treated with a solution of bromoacetyl bromide (4.2g) in dry tetrahydrofuran (10ml). After 1h the solvent was removed under reduced pressure and the residue taken up in water and acidified to pH3. The acidic solution was extracted into ethyl acetate, dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Recrystallisation from isopropanol afforded the product as white needles: mp 112-114°C.

(b) (2S, 3S)-3-(3,5-Bis(trifluoromethyl)phenyl)methyloxy)-1-(N-methanesulfonyl)carboxamidomethyl)-2-phenylpiperidine

Diispropylethylamine (187mg) was added to a stirred solution of N-bromoacetylmethanesulfonamide (42mg) and the compound of Description 3 (300mg) in dry acetonitrile (10ml). The resulting solution was stirred for 18h at room temperature. Solvent was removed under reduced pressure and the residue partitioned between ethyl acetate and water. The organic layers were separated, dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Recrystallisation from ether/hexane afforded the product as a white powder: mp 127-130°C.
$C_{23}H_{24}N_2O_4F_6 \cdot 0.25H_2O$ requires C, 50.87; H, 4.55; N, 5.16.
Found: C, 50.73; H, 4.38; N, 5.07%.

The following examples illustrate pharmaceutical compositions according to the invention.

EXAMPLE 18A Tablets containing 1-25mg of compound

| | Amount mg | | |
|---|---|---|---|
| Compound of formula (I) | 1.0 | 2.0 | 25.0 |
| Microcrystalline cellulose | 20.0 | 20.0 | 20.0 |
| Modified food corn starch | 20.0 | 20.0 | 20.0 |
| Lactose | 58.5 | 57.5 | 34.5 |
| Magnesium Stearate | 0.5 | 0.5 | 0.5 |

EXAMPLE 18B Tablets containing 26-100mg of compound

| | Amount mg | | |
|---|---|---|---|
| Compound of formula (I) | 26.0 | 50.0 | 100.0 |
| Microcrystalline cellulose | 80.0 | 80.0 | 80.0 |
| Modified food corn starch | 80.0 | 80.0 | 80.0 |
| Lactose | 213.5 | 189.5 | 139.5 |
| Magnesium Stearate | 0.5 | 0.5 | 0.5 |

The compound of formula (I), cellulose, lactose and a portion of the corn starch are mixed and granulated with 10% corn starch paste. The resulting granulation is sieved, dried and blended with the remainder of the corn starch and the magnesium stearate. The resulting granulation is then compressed into tablets containing 1.0mg, 2.0mg, 25.0mg, 26.0mg, 50.0mg and 100mg of the active compound per tablet.

EXAMPLE 19 Parenteral injection

| | Amount mg |
|---|---|
| Compound of formula (I) | 1 to 100mg |
| Citric Acid Monohydrate | 0.75mg |
| Sodium Phosphate | 4.5mg |
| Sodium Chloride | 9mg |
| Water for Injections | to 1ml |

The sodium phosphate, citric acid monohydrate and sodium chloride are dissolved in a portion of the water. The compound of formula (I) is dissolved or suspended in the solution and made up to volume.

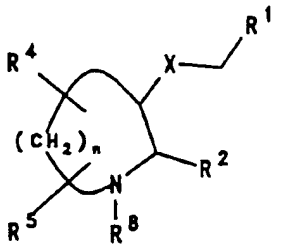
EXAMPLE 20 Topical formulation

| | Amount mg |
|---|---|
| Compound of formula (I) | 1-10g |
| Emulsifying Wax | 30g |
| Liquid paraffin | 20g |
| White Soft Paraffin | to 100g |

The white soft paraffin is heated until molten. The liquid paraffin and emulsifying wax are incorporated and stirred until dissolved. The compound of formula (I) is added and stirring continued until dispersed. The mixture is then cooled until solid.

**CLAIMS:**

1. A compound of formula (I), or a salt of prodrug thereof:



(I)

wherein

n is 1, 2 or 3;

X represents O or S;

$R^1$ represents phenyl optionally substituted by 1, 2 or 3 groups selected from $C_{1-6}$alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$alkynyl, halo, cyano, nitro, trifluoromethyl, trimethylsilyl, $-OR^a$, $SR^a$, $SOR^a$, $SO_2R^a$, $-NR^aR^b$, $-NR^aCOR^b$, $-NR^aCO_2R^b$, $-CO_2R^a$ and $-CONR^aR^b$;

$R^2$ represents aryl selected from phenyl and naphthyl; heteroaryl selected from indazolyl, thienyl, furyl, pyridyl, thiazolyl, tetrazolyl and quinolyl; benzhydryl; or benzyl; wherein each aryl or heteroaryl moiety may be substituted by $C_{1-6}$alkyl, $C_{1-6}$alkoxy, halo or trifluoromethyl;

$R^4$ and $R^5$ may be present on any available carbon atom of the azacyclic ring and each independently represent H, halo, $C_{1-6}$alkyl, oxo, $CH_2OR^a$, $CO_2R^a$ or $CONR^aR^b$;

$R^8$ represents $C(COOR^a)_2$, $C(CONR^aR^b)_2$ or $C_{1-6}$alkyl substituted by $C(=NR^a)NR^bNR^cCO_2R^d$, $CONHNR^aR^b$,

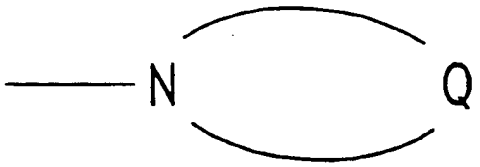
$C(S)NR^aR^b$, $CONR^aC_{1-6}alkylR^{12}$, $CONR^{13}C_{2-6}alkynyl$, $CONR^{13}C_{2-6}alkenyl$, $COCONR^aR^b$, $CONR^aC(NR^b)NR^cR^d$, $CONR^{13}SO_2R^a$, $SO_2NR^{13}COR^a$, $CONR^a$heteroaryl or $COR^q$;

$R^a$, $R^b$, $R^c$ and $R^d$ each independently represent H, $C_{1-6}$alkyl, phenyl or trifluoromethyl.

$R^{12}$ represents $OR^a$, $CONR^aR^b$ or heteroaryl;

$R^{13}$ represents H or $C_{1-6}$alkyl; and

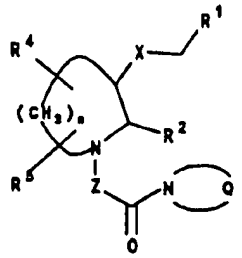
$R^q$ represents a group



where Q represents the residue of a non-aromatic azacyclic or azabicyclic ring system.

2. A compound as claimed in claim 1 wherein $R^4$ and $R^5$ each independently represent H, halo, $C_{1-6}$alkyl, oxo, $CO_2R^{10}$ or $CONR^{10}R^{11}$; $R^8$ represents $C_{1-6}$alkyl substituted by a group selected from $CONHNR^aR^b$, $C(S)NR^aR^b$, $CONR^aC_{1-6}alkylR^{12}$, $CONR^{13}C_{2-6}alkynyl$, $CONR^{13}C_{2-6}alkenyl$, $COCONR^aR^b$, $CONR^aC(NR^b)NR^aR^b$, and $CONR^a$heteroaryl; or a salt or prodrug thereof.

3. A compound as claimed in claim 1 of formula (Ia):



(Ia)

wherein n, X, $R^1$ and $R^2$ are as defined for formula (I); Q is the residue of an azacyclic or a bridged azabicyclic ring system;

Z represents an alkyl chain of 1, 2, 3, 4, 5 or 6 carbon atoms; and

$R^4$ and $R^5$ each independently represent H, halo, $C_{1-6}$alkyl, oxo, $CO_2R^a$ or $CONR^aR^b$; or a salt or prodrug thereof.

4. A compound as claimed in claim 1 wherein $R^8$ represents $C(COO(C_{1-6}alkyl))_2$, $C(CONH_2)_2$ or $C_{1-6}$alkyl substituted by $C(=NH)NHNHCO_2C_{1-6}alkyl$, $CONHNH_2$, $COCONH_2$, $CONHC(NH)NH_2$, $CSNH_2$, $CONR^{13}C_{2-6}alkynyl$, $COR^9C_{1-6}alkylC_{1-6}alkoxy$, $CONHSO_2C_{1-6}alkyl$, $CONR^aC_{1-6}alkylheteroaryl$, $CONR^a$heteroaryl or $COR^q$.

5. A compound as claimed in any preceding claim wherein n is 3.

6. A compound as claimed in any preceding claim wherein X is O.

7. A compound as claimed in any preceding claim wherein $R^1$ represents phenyl substituted by 1, 2 or

3 groups selected from $C_{1-4}$alkyl, trifluoromethyl and halo.

8. A compound as claimed in any preceding claim wherein $R^2$ represents benzhydryl or phenyl optionally substituted by halo.

9. A compound as claimed in claim 1 selected from
(2R*,3R*)-3-((3,5-bis(trifluoromethyl)phenyl)methyloxy)-2-phenyl-1-(N-(prop-2-ynyl)carboxamidomethyl)piperidine;
(2R*,3R*)-3-((3,5-bis(trifluoromethyl)phenyl)methyloxy)-1-(N-furfuryl)carboxamidomethyl)-2-phenylpiperidine;
(2R*,3R*)-3-((3,5-bis(trifluoromethyl)phenyl)methyloxy)-2-phenyl-1-(N-(3-pyridylmethyl)carboxamidomethyl) piperidine;
(2R*,3R*)-3-((3,5-bis(trifluoromethyl)phenyl)methyloxy)-1-(N-(2-methoxyethyl)carboxamidomethyl)-2-phenyl piperidine;
(2R*,3R*)-3-((3,5-bis(trifluoromethyl)phenyl)methyloxy)-1-(carboxyhydrazidomethyl)-2-phenylpiperidine;
(2S,3S)-1-(N-amidino(carboxamidomethyl))-3-((3,5-bis(trifluoromethyl)phenyl)methyloxy)-2-phenylpiperidine;
(2S,3S)-3-((3,5-bis(trifluoromethyl)phenyl)methyloxy)-2-phenyl-1-[N-methyl-N-((3-pyridylmethyl) carboxamidomethyl)]piperidine;
(2S,3S)-3-((3,5-bis(trifluoromethyl)phenyl)methyloxy)-1-(2-morpholino-2-oxo)ethyl-2-phenylpiperidine;
(2S,3S)-3-((3,5-bis(trifluoromethyl)phenyl)methyloxy)-1-(2-oxo-2-piperidino)ethyl-2-phenylpiperidine;
(2S,3S)-3-((3,5-bis(trifluoromethyl)phenyl)methyloxy)-1-(2-oxo-2-(4-methylpiperazinyl))ethyl-2-phenylpiperidine;
(2R*,3R*)-3-benzyloxy-1-(2-morpholino-2-oxo)ethyl-2-phenylpiperidine;

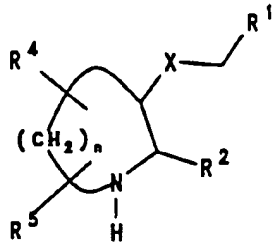
(2R*,3R*)-3-((3,5-bis(trifluoromethyl)phenyl)methyloxy)-2-phenyl-1-(thiocarboxamidomethyl)piperidine;
(2S,3S)-3-((3,5-bis(trifluoromethyl)phenyl)methyloxy)-2-phenyl-1-(N-(2-pyridylmethyl)carboxamidomethyl) piperidine;
2-[(2S,3S)-3-((3,5-bis(trifluoromethyl)phenyl)methyloxy)-2-(diphenylmethyl)pyrrolidino]-N-(carbomethoxy)acetamidrazone;
(2S,3S)-3-((3,5-bis(trifluoromethyl)phenyl)methyloxy)-1-bis(carbomethoxy)methyl-2-phenylpiperidine;
(2S,3S)-3-((3,5-bis(trifluoromethyl)phenyl)methyloxy)-1-bis(carboxamido)methyl-2-phenylpiperidine;
(2S,3S)-3-((3,5-bis(trifluoromethyl)phenyl)methyloxy)-1-(N-methanesulfonyl)carboxamidomethyl)-2-phenylpiperidine;
and salts and prodrugs thereof.

10. A compound as claimed in any preceding claim for use in therapy.

11. A pharmaceutical composition comprising a compound as claimed in any of claims 1 to 9 in association with a pharmaceutically acceptable carrier.

12. A process for the preparation of a compound as claimed in claim 1 which process comprises

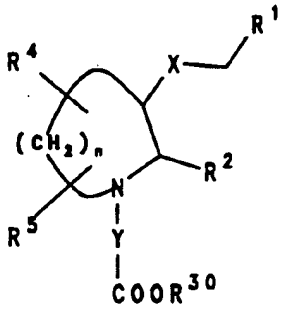
(A) reacting a compound of formula (II):



(II)

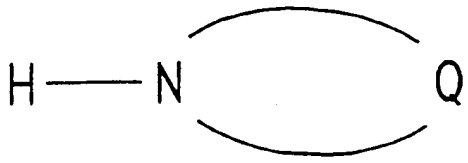
wherein $R^1$, $R^2$, $R^4$, $R^5$, X and n are as defined for formula (I) with a reagent suitable to introduce the group $R^8$; or

(B) reacting an intermediate of formula (III):



(III)

wherein $R^1$, $R^2$, $R^4$, $R^5$, X and n are as defined for formula (I), $R^{30}$ is H or alkyl and Y represents $C_{1-6}$alkylidene with an amine of formula $HNR^aC_{1-6}alkylR^{12}$, $HNR^{13}C_{2-6}$alkenyl, $HNR^{13}C_{2-6}$alkynyl, $HNR^aC(NR^b)NR^cR^9$, $HNR^a$heteroaryl or



in the presence of a base;

and optionally forming a salt or prodrug.

13. A method for the treatment or prevention of a physiological disorder associated with an excess of tachykinins, which method comprises administration to a patient in need thereof of a tachykinin-reducing amount of a compound according to claim 1.

14. A method according to claim 13 for the treatment or prevention of pain or inflammation.

15. A method according to claim 13 for the treatment or prevention of migraine.

16. A method according to claim 13 for the treatment or prevention of arthritis.

17. The use of a compound as claimed in claim 1 for the manufacture of a medicament for the treatment of a physiological disorder associated with an excess of tachykinins.

18. The use of a compound as claimed in claim 1 for the manufacture of a medicament for the treatment of pain or inflammation.

19. A compound as claimed in any of claims 1 to 10 when prepared by the process of claim 12.

20. A process for preparing a composition as claimed in claim 11 which process comprises bringing a compound as claimed in any of claims 1 to 9 into association with a pharmaceutically acceptable carrier or excipient.

# INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 93/01525

## I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07D211/42; C07D401/12; C07D207/12; C07D211/54
A61K31/445; A61K31/40

## II. FIELDS SEARCHED

Minimum Documentation Searched[7]

| Classification System | Classification Symbols |
|---|---|
| Int.Cl. 5 | C07D ; A61K |

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

## III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

| Category ° | Citation of Document,[11] with indication, where appropriate, of the relevant passages[12] | Relevant to Claim No.[13] |
|---|---|---|
| Y | EP,A,0 436 334 (PFIZER INC)<br>10 July 1991<br>cited in the application<br>*see definitions of R6 and R8* | 1-12,<br>17-20 |
| P,X | EP,A,0 528 495 (MERCK SHARP & DOHME LTD.)<br>24 February 1993<br>cited in the application<br>*see especially definition of R8 on page 4, line 27, i.e. alkyl substiuted by COCONR10R11* | 1,2,4-8,<br>10-12,<br>17-20 |
| P,Y | | 1-12,<br>17-20 |
| P,A | EP,A,0 499 313 (MERCK SHARPE & DOHME)<br>19 August 1992 | 1-12,<br>17-20 |

-/--

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified).

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

## IV. CERTIFICATION

| Date of the Actual Completion of the International Search | Date of Mailing of this International Search Report |
|---|---|
| 09 NOVEMBER 1993 | 25. 11. 93 |
| **International Searching Authority** | **Signature of Authorized Officer** |
| EUROPEAN PATENT OFFICE | SCRUTON-EVANS I. |

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

| Category ° | Citation of Document, with indication, where appropriate, of the relevant passages | Relevant to Claim No. |
|---|---|---|
| P,Y | JOURNAL OF MEDICINAL CHEMISTRY<br>vol. 35, no. 26, 1992,<br>pages 4911 - 4913 'Discovery of a potent substance P antagonist: recognition of the key molecular determinant'<br>--- | 1-12,<br>17-20 |
| X | CHEMICAL ABSTRACTS, vol. 100,<br>1984, Columbus, Ohio, US;<br>abstract no. 192245m, 'The synthesis of peptide beta-lactams as potential protease inhibitors'<br>page 619 ;<br>see abstract<br>& JOURNAL OF THE CHEMICAL SOCIETY., PERKIN TRANS 1<br>vol. 1, 1984,<br>pages 29 - 39<br>*see compounds of formula I*<br>----- | 1,3,4,6,<br>7 |

# ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

GB 9301525
SA 77499

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on
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| Patent document cited in search report | Publication date | Patent family member(s) | | Publication date |
|---|---|---|---|---|
| EP-A-0436334 | 10-07-91 | WO-A- | 9109844 | 11-07-91 |
| | | EP-A- | 0558156 | 01-09-93 |
| EP-A-0528495 | 24-02-93 | AU-A- | 2413892 | 16-03-93 |
| | | WO-A- | 9304040 | 04-03-93 |
| EP-A-0499313 | 19-08-92 | JP-A- | 5078354 | 30-03-93 |
| | | US-A- | 5242930 | 07-09-93 |
| | | CA-A- | 2060949 | 12-08-92 |